REMARKS

Amendments

Because the Advisory Action indicated that the amendments presented with the Response After Final dated January 21, 2010, would not be entered, the amendments as presented herein are shown relative to the specification and claims as pending prior to that Response.

Amendment to the Specification

The "STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH" section of the specification has been amended to be in accordance with 35 U.S.C. 202 (c) (6). No new matter has been added.

Amendments to the Claims

Claim 11 is amended. Support for the claim amendment can be found throughout the application as originally filed, e.g., at page 23, lines 27-29. No new matter has been added.

Claims 20 and 35 have been cancelled without prejudice or disclaimer.

Applicants note that entry of the claim amendments submitted herein is proper, because the amendments merely cancel claims or present claims in better form for appeal. Entry of the amendments is respectfully requested.

Upon entry of this amendment, claims 11, 16-19, and 22-34 are pending in the application.

Interview Summary

Applicants thank Examiners McMillian and Padmanabhan for their courtesy in allowing a telephonic interview with the undersigned representative on March 16, 2010 (the "Interview"). During the Interview, the pending claims and outstanding rejections were discussed. Applicants proposed certain amendments, which the Examiners agreed to consider. The Examiners agreed that the subject matter of previously-proposed claim 36 appeared to overcome the rejections of record, but no final agreement was reached.

Rejections Under 35 U.S.C. § 103

(i) In the Office Action, claims 11, 16-20, 22-26 and 33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury et al., U.S. Patent No. 5,589,480, in view of Elden, U.S. Patent No. 5,814,659, and further in view of Saito et al. (Anesthesiology, Vol. 89(6)) and Goodman and Gilman. Applicants respectfully disagree and traverse this rejection.

The present claims are directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. Amended claim 11 (from which all remaining claims depend) recites that the morphine and butamben are present in a ratio of about 0.4.

According to the Office Action, Elkhoury teaches "the topical administration of an opioid drug, such as morphine, to produce an analgesic effect in a localized peripheral area." The Office Action further stated that Elkhoury teaches that "morphine and other opioids can produce potent analgesic effects after local application to peripheral tissue." However, the Office Action explicitly concedes that Elkhoury does not teach or suggest the use of butamben together with morphine. Applicants further point out that Elkhoury lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

Elden (U.S. Patent No. 5,814,659) cannot remedy the deficiencies of Elkhoury. The present Office Action states that Elden teaches topical analgesic compositions and methods for inducing topical analgesia, and topical compositions including butamben picrate. However, Elden does not teach or suggest the use of butamben together with morphine. Applicants further point out that Elden lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. Even if the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there is no expectation of their synergistic effect in the periphery. The Office Action states that combining "two compositions . . . useful for the same purpose, in order to form a third composition to be used for the very same purpose" is *prima facie* obvious. Even if that were true, a synergistically effective

composition would not be *prima facie* obvious. Elden, alone or in combination with Elkhoury, cannot render obvious the presently-pending claims.

Saito purportedly teaches the synergistic effects of morphine and lidocaine or bupivacaine when systemically administered via bolus injection or continuous coinfusion. Saito does not teach the administration of butamben. Similarly, Saito does not teach the topical administration of these compounds nor does Saito suggest that the synergistic effect would be retained in the periphery via topical administration. Saito does not and cannot render obvious the claimed subject matter by itself, and the prior Office Action does not allege that Saito alone renders the claimed subject matter unpatentable. Saito cannot remedy the deficiencies of Elkhoury and/or Elden, whether taken alone or in any combination.

The Office Action cites the Goodman reference as teaching that some local anesthetics have common activities, and that benzocaine and butamben can be applied topically. In any event, the prior Office Action does not suggest that Goodman teaches that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. The prior Office Action points to nothing in Goodman that could teach or suggest that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. Goodman cannot remedy the deficiencies of Elkhoury and/or Elden and/or Saito, whether taken alone or in any combination.

Although the current Office Action appears to take the position that synergism in the periphery would be expected based on synergism for systemically administered drugs (see, e.g., Office Action at page 3), Applicants disagree. Even if synergism for systemically administered drugs were known, synergism for topically administered drugs was not known at the time the invention was made, and would not have been predictable. When acting centrally, drugs can have many possible locations to act; however, in the periphery, it is necessary for two drugs to act on the same axon to have a synergistic effect. That two topically-administered drugs could act synergistically would not have been expected at the time the invention was made.

The Office Action stated that "in the absence of unexpected results, an ordinarily skilled artisan would reasonably expect that the combination would also produce synergism when combined in the periphery." Applicants do not agree.

As noted above, even if Saito discloses synergy of certain compounds administered systemically, there would be no reasonable expectation that synergy would exist when compounds are administered peripherally. It is respectfully submitted that the topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected to one of skill in the art of pain management at the time the present invention was made. Prior to the teachings of the instant application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

First, as detailed at length in the Response filed August 16, 2007 (which is incorporated herein by reference), several medical reports published before the filing of the present application teach that methods comprising the topical use of morphine fail to stimulate peripheral sites. As described previously, the Raja *et al.* (Anesthesiology 77:1143-7; 1992), Rosenstock *et al.* (Ref. Anesth. 21:93-8; 1996), Picard *et al.* (Pain 72:309-18; 1997), and Yarussi et al., (Reg. Anesth. Pain. Med. 24:142-5; 1999) references described various studies in which peripheral analgesia was not seen with morphine. Although the Office Action points to Elkhoury as teaching that "topical administration of morphine produces analgesia in the periphery," Applicants submit that, even if that is true, "[w]hen prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill." In re Young, 927 F.2d 588 (Fed. Cir. 1991).

Second, the Declaration of Sandra C. Roerig, Ph.D., submitted in related application No. 09/975,812 (now U.S. Patent No. 6,790,855) and discussed in the Response filed August 16, 2007, provided evidence that, prior to the invention of the claimed subject matter, scientists did not expect that morphine and lidocaine would

synergistically potentiate the antinociceptive effects of each other in the periphery. The Office Action does not discuss this Declaration other than to say that:

> This declaration is not persuasive because it lacks any further explanation. No data or explanation was presented to support the conclusions stated. Furthermore the declaration does not mention action in the periphery as compared to systemic action.
> Office Action at page 5.

Applicants disagree. The Declaration provides clear evidence that the claimed subject matter was not obvious at the time the invention was made. The Declaration, made by a person knowledgeable about the state of the art at the time, and discussing reaction of additional skilled persons to certain data disclosed in the present application, provides clear evidence that persons skilled in the art at the time the invention was made found the subject matter to be surprising and non-obvious. In addition, the MPEP provides that "'some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him.'" MPEP 716.01(c)(III) (citation omitted).

Third, the Office Action stated that combining "two compositions . . . useful for the same purpose, in order to form a third composition to be used for the very same purpose" is *prima facie* obvious. Even if that were true, a synergistically effective composition would not be *prima facie* obvious. Saito does not rectify this deficiency, for at least the reason that any synergism of Saito in systemic administration would not be expected when administered topically to peripheral sites, as discussed above. Moreover, as the Office Action acknowledges, data has been provided showing that the combination of morphine and butamben provides synergistic effects upon peripheral administration. Applicants point out that the present application provides additional examples of synergistic combinations of morphine and a topical anesthetic (see, e.g., the Examples). In addition, Applicants note that the present claims recite that the administered pharmaceutical composition comprises synergistically effective amounts of morphine and butamben. Applicants contend that the showing of synergism confirms the unexpectedly superior properties of the methods as presently claimed. Additionally, as discussed at the Interview, the Examiners agreed that the subject matter of

previously-proposed claim 36 appeared to overcome the rejections of record, but no final agreement was reached. Claim 11 as now pending recites that morphine and butamben are present in a ratio of about 1:0.4, a ratio for which the Office Action has acknowledge that synergism has been demonstrated.

Finally, the Office Action discusses the Kolesnikov et al. journal article (Anesth. Anal. (2003), volume 97, pp. 1103-1107) and concludes that "the synergistic effects of topical lidocaine and morphine were not unexpected." Applicants disagree. It will be appreciated that the cited Kolesnikov et al. article was published in 2003, well after the effective filing date of the present application (which claims priority to a provisional application filed in April, 2000 and a utility application filed in April, 2001). Although the Office Action concedes that the Kolesnikov et al. journal article (published in 2003) is not prior art, Applicants further point out that the Kolesnikov et al. journal article was published after the effective filing date of the present application (and after the publication of the priority application USSN 09/844,111) and therefore cannot provide any evidence that the claimed subject matter would have been obvious to one of ordinary skill in the art at the time the priority application(s) were filed, nor at the time the presently-claimed invention was made. Contrary to the statement in the Office action ("Thus [based on Kolesnikov et al.] there is a reasonable expectation of success that when butamben is administered topically with morphine, a synergistic effect would occur and therefore the synergistic results as claimed . . . is not unexpected."), the post-filing Kolesnikov et al. journal article cannot be used as evidence to show that there was a reasonable expectation of success as of the time the invention was made (or at the effective filing date of the present application).

From the foregoing it can be seen that none of the cited references, whether taken alone or in any combination, teaches or suggest the combination of features of the presently-claimed subject matter, in which a method of providing topical analgesia to a subject includes topically administering to peripheral sites in the subject a pharmaceutical composition comprising (i) synergistically effective amounts of morphine and butamben and (ii) a physiologically acceptable topical excipient, to potentiate analgesia at the peripheral sites.

Applicants respectfully contend that the Office Action does not even make out a *prima facie* case of obviousness of the present claims. Reconsideration and withdrawal of the rejection is proper and the same is requested.

(ii) In the Office Action, claims 27-32 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury, Elden, Saito, and Goodman as applied to claims 11, 16-20, 22-26, and 33 above, and further in view of Mayer et al. Claims 34-35 were rejected under 35 U.S.C. § 103 as being unpatentable over Elkhoury, Elden, Saito, and Goodman as applied to claims 11, 16-20, 22-26, and 33 above, and further in view of Soo et al. Again, Applicants disagree.

As stated above, the pending claims are directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

As discussed in detail above, claims 11-13, 16-19, 26, and 33 are nonobvious in view of the combination of the cited references. Claims 27-32, and 34 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Moreover, the further combination of either Mayer or Soo with the combination of Elkhoury, Elden, Saito, and Goodman fails to remedy the deficiencies of those references as described above. While the Office Action states that Mayer teaches "compositions comprising . . . an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof," the Office Action does not allege that Mayer teaches compositions comprising butamben, much less providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. Similarly, while the Office Action states that Soo "teaches that "morphine is known in the art for the treatment of peripheral neuropathy," Soo is silent as to compositions comprising butamben, does not teach or suggest administration of synergistically effective amounts of morphine and butamben, does not teach or suggest peripheral administration of morphine or butamben, and does not teach or suggest providing, to

peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. The additional references, whether taken alone or in any combination, with any or all of the other cited references, cannot render obvious any of the pending claims.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants believe the pending application is in condition for allowance. Early and favorable action is earnestly requested.

Applicants conditionally petition for any extension of time necessary for consideration of this response. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 62069DIV2 (51590).

Respectfully submitted,

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